



Review

A Review of hormone-based therapies to treat adult acne vulgaris in women



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ABSTRACT

Hormone-based therapies including combined oral contraceptive medications and spironolactone are considered effective therapies to treat adult acne in women. Our objective is to provide a concise and comprehensive overview of the types of hormonal therapy that are available to treat acne and comment on their efficacy and safety profiles for clinical practice. A systematic search using the PubMed Database was conducted to yield 36 relevant studies for inclusion in the review and several conclusions were drawn from the literature.

Treatment with oral contraceptive pills leads to significant reductions in lesion counts across all lesion types compared with placebo. There were no consistent differences in efficacy between the different combined oral contraceptive formulations. In terms of risk, oral contraceptive pill users had three-times increased odds of venous thromboembolism versus non-users according to a recent meta-analysis (95% confidence interval 2.46–2.59). Data on oral contraceptive pill use and breast cancer risk are conflicting but individual patient risk factors and histories should be discussed and considered when prescribing these medications. However, use of these medications does confer measurable protection from endometrial and ovarian cancer. Spironolactone was also shown to be an effective alternative treatment with good tolerability. Combined oral contraceptive medications and spironolactone as adjuvant and monotherapies are safe and effective to treat women with adult acne. However, appropriate clinical examinations, screening, and individual risk assessments particularly for venous thromboembolism risk must be conducted prior to initiating therapy.

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Introduction

Background

Acne in women over the age of 25 years, also known as adult-onset or persistent acne, affects approximately 12 to 22% of women in the United States. Historically, acne vulgaris has been primarily associated with the adolescent population. However, the burden of disease in the adult population has been highlighted in recent literature and women are noted to have greater incidence of disease compared with their male counterparts (Tanghetti et al., 2014). It should be noted that a number

of adult women with acne may have underlying polycystic ovarian syndrome (PCOS) because approximately 70 to 80% of patients with PCOS suffer from cutaneous manifestations of the disease (Schmidt et al., 2015).

Adult acne in women is often associated with anxiety, depression, and a reduced quality of life (Tanghetti et al., 2014). Furthermore, this condition is characterized by high rates of treatment failure. In one prospective study of 200 women over the age of 25 years, approximately 80% of women failed multiple courses of systemic antibiotic medications and approximately 30% of patients relapsed after several therapeutic cycles of isotretinoin (Goulden et al., 1997). The high rates of treatment failure with traditional therapies along with more consciousness about antibiotic stewardship in dermatology patients, many of whom are on systemic antibiotic therapy for acne treatment, have motivated clinicians to reconsider the therapeutic targets of treatment in this population (Dreno et al., 2014).

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There is considerable evidence on the role of sex hormones and specifically relative to androgen excess in the pathophysiology of acne vulgaris. For example, the development of acne in pre-pubertal girls has been correlated with high levels of dihydroepiandrosterone sulfate. Polycystic ovarian syndrome in which women experience hyperandrogenism is also associated with an increased prevalence of acne vulgaris. Individuals who are androgen insensitive do not experience acne. Most importantly and perhaps the strongest evidence is the effective use of combined oral contraceptive medications and anti-androgen therapies to treat women for acne. Hormonal therapy has been shown to be effective in postmenarchal adult women (age >14 years) even in those women with normal androgen levels (Harper, 2008; Lolis et al., 2009; Lucky et al., 1991, 1994, 1997).

Objective

A myriad of combined oral contraceptive (COC) formulations and anti-androgen therapies exist and have been used in the clinical setting for the treatment of acne vulgaris with various efficacies and side effect profiles. The main objective of this systematic review is to provide a broad overview of currently available therapies and their efficacies, risks, side effects, and contraindications as reported by controlled clinical trials to date. Important counseling points for patients prior to the initiation of hormonal therapy and other types of contraception and their implications for acne are discussed.

Methods

A systematic search of the PubMed Database was conducted with the following search terms: contraceptives, hormone therapy, spironolactone, flutamide, and acne treatment. The terms polycystic ovarian syndrome, endometriosis, and hidradenitis suppurativa were excluded from the search. Filters included human studies that were published after January 1, 2000. A total of 236 results were then manually filtered with a systematic approach to exclude review papers, unrelated topics, commentaries, and articles that were published in a language other than English, which yielded 36 relevant studies.

General principles

Hormonal therapy is often considered to treat acne vulgaris in the settings of hyperandrogenism, late-onset acne (>25 years of age), jawline acne distribution, acne with menstrual flare, comedonal acne with seborrhea, and acne that is resistant to conventional therapies. Prior to the initiation of hormone therapy, expectations about long-term systemic treatment should be set in terms of family planning. Additionally, an endocrinologic evaluation should be prompted by certain clinical signs and symptoms including hirsutism, androgenetic alopecia, virilization, acanthosis nigricans, central obesity, oligo- or amenorrhea, infertility, sudden and/or severe onset acne, and acne that is significantly resistant to conventional therapy (Zaenglein et al., 2016). It should also be noted that antiandrogen therapy should always be used with an effective contraceptive method if the patient can get pregnant (Fausser et al., 2012). Hormonal therapy to treat acne may take longer to show results compared with other acne treatments and often requires 3 months to 6 months of treatment for efficacy (Koo et al., 2014). Therefore, it is important to set appropriate expectations for patients prior to treatment initiation.

Types of hormone therapies

Hormone-based therapies can be separated into two broad categories: androgen synthesis inhibitors and androgen receptor antagonists. Estrogen and progesterone derivatives, which make up the components of COC medications, are generally considered androgen synthesis inhibitors. Commonly known androgen receptor antagonists include agents such as spironolactone, flutamide, cyproterone acetate, and progestins alone (Trifu et al., 2011). We will consider COC medications, spironolactone, and flutamide separately with regard to their use to treat patients with adult acne. We will briefly discuss the use of metformin although its use to treat adult acne is not formally reviewed in this paper.

Combined oral contraceptive medications

Oral contraceptive medications are thought to primarily exert anti-androgen effects through the actions of estrogen. Estrogen is known to stimulate the hepatic synthesis of sex hormone and bind globulin, which binds androgens and decreases levels of free testosterone, with dihydroepiandrosterone sulfate. Estrogen also inhibits 5- α reductase, which prevents the conversion of testosterone to the more potent dihydrotestosterone. Ovarian and adrenal androgen synthesis is also reduced due to the effects of estrogen and its negative feedback on gonadotropin, which releases hormone and leutinizing hormone (Haider and Shaw, 2004). Progestins have a lesser role in the production of anti-androgenic activity because early generation progestins have androgenic properties. When choosing oral contraceptive pills (OCPs) for the treatment of acne, third generation progestins (e.g., norgestimate or desogestrel) or later generations (e.g., fourth or fifth generation progestin-containing OCP formulations) are preferred because they have a lower androgenic activity overall. Progestins may contribute to the anti-androgenic properties of combined oral contraceptive medications through the reduction of gonadotropin-releasing hormone pulsatility and therefore luteinizing hormone production (Arowojolu et al., 2012).

Although numerous formulations of oral contraceptive medications exist, the U.S. Food and Drug Administration (FDA) has only approved three medications to date for the treatment of acne vulgaris: Ortho Tri-Cyclen (combination of norgestimate and ethinyl estradiol [EE]), Estrostep (combination of norethindrone acetate and EE), and Yaz (combination of drospirenone and EE; Ebede et al., 2009). A number of clinical trials on the safety and efficacy of different COC formulations to treat acne vulgaris have been published to date. Table 1 consolidates this evidence by COC formulation, duration of study, type of study, dosages used, and published results. To date, the superiority of particular OCP formulations for the treatment of acne have not been clearly demonstrated.

Multiple COC formulations have been studied in the context of treating adult women with acne vulgaris. All combinations that are reported in Table 1 exhibit some degree of efficacy in the reduction of acne lesion count. In terms of adverse events in patients with acne who were treated with COC medications, the most commonly reported events include headache, menstrual cycle irregularities, and emotional lability. Three of the studies reported severe adverse events related to COC use, with two cases of clinical depression and one case of ovarian cyst formation. However, the most common side effects that were reported in these studies are well known and expected for low-dose combined oral contraceptive medications. None of the studies reported above demonstrated any unexpected adverse events.

In terms of comparing efficacies, desogestrel may be slightly more effective than levonorgestrel COC formulations. However, one of the three comparison studies reported that the two have equal efficacy. The chlormadinone acetate (CMA) formulation may be more

efficacious than levonorgestrel. However, CMA has not been marketed in the United States since 1972 after reports of mammary gland nodule formation in a study using canines. Several European countries, however, still use CMA COC formulations (Lingeman, 2012). All other comparison studies revealed results of non-inferiority. Studies that compared COC formulations head-to-head and had relevant results are listed in Table 2. A meta-analysis of 24 randomized trials that was conducted by Arowojolu et al., 2012 demonstrated no consistent differences in acne reduction between different combined OCPs (Arowojolu et al., 2012).

Counseling for patients: Risks, benefits, and contraindications

COC formulations can provide significant relief to patients who suffer from severe acne vulgaris, especially when conventional therapy has failed. However, to achieve maximum benefits and safety for each individual patient, counseling and discussion must be pursued during the initial visit. Contrary to previous practice, pelvic examinations and Pap smears are not required prior to prescribing COC medications according to recommendations by the World Health Organization, the American Congress of Obstetricians and Gynecologists (ACOG), and Planned Parenthood. This makes it more feasible for dermatologists to prescribe COC medications during routine clinic visits (Frangos et al., 2008). Patients commonly ask about cardiovascular, clotting, and cancer risks that are associated with oral contraceptive use. These issues are addressed separately below.

Cardiovascular risk

When counseling patients about cardiovascular risk, it is important to address modifiable risk factors such as smoking, hypertension, and diabetes and how control of these factors are the most important in reducing long-term risks of myocardial infarction and stroke. The risk of clotting should be discussed in context of baseline risks for women in the general population. The risk of deep vein thrombosis in women at baseline is 1/10,000 woman-years; at 1 year of COC use 3.4/10,000 woman-years; and during pregnancy 5 to 12/10,000. Peragallo Urrutia et al. (2013) conducted a meta-analysis of 14 different studies in which OCP users had three times increased odds for venous thromboembolism (VTE) compared with non-users.

Interestingly, older progestins seem to confer a lower VTE risk than newer progestin-based COC formulations. In 2012, drospirenone-based COC formulations were FDA-labeled with a warning for an increased risk of clotting (Lidegaard et al., 2012; Manzoli et al., 2012). However, this was contradicted when the results of a prospective controlled trial entitled "Long-term active surveillance study for oral contraceptives" were published in 2016 and demonstrated that drospirenone-based OCPs did not pose a higher risk for VTE compared with other OCPs (Dinger et al., 2016). In summary, there is a slightly increased risk of DVT in COC users but much less than that of the thrombophilic state of pregnancy.

Cancer risk

In 1996, the Collaborative Group on Hormonal Factors in Breast Cancer conducted a meta-analysis of 54 different epidemiological studies in which data from 53,297 women with breast cancer and 100,239 women without breast cancer was analyzed. The findings suggested a slightly increased risk of breast cancer in women who take a COC formulation (relative risk = 1.24, 95% confidence interval [CI]). This risk was increased up to 10 years after discontinuing birth control but did not extend past this time frame. Notably, women who were diagnosed with breast cancer and had taken

COC medications had clinically less advanced tumors compared with women who were diagnosed with breast cancer and had not taken COC formulations (Collaborative Group on Hormonal Factors in Breast Cancer, 1996).

The more recent 2002 Women's CARE study in which 4575 women were interviewed demonstrated contrary to the previously mentioned pooled analysis that there was no significant increase in the risk of breast cancer in COC users between the ages of 35 and 64 years (relative risk = 1.0). Similar to the pooled analysis study, the risk of breast cancer was not significantly related to the dose of estrogen or duration of COC use (Marchbanks et al., 2002). However, a 36-year follow-up in the Nurse's Health Study, which aimed to assess the risk of breast cancer with COC use, reported a higher risk of premature deaths due to breast cancer in the population that used COC formulations ($p < .0001$). The authors hypothesized that this higher risk may be attributable to higher hormone doses that were used in earlier COC formulations (Charlton et al., 2014).

The risk of breast cancer with COC use is still controversial because these major studies have inconsistent outcomes. When discussing the risk with patients, it is important to highlight that the long-term risks remain unclear at this time. Newer formulations of OCPs use 5- to 10-fold less hormone than the original formulations so more data is needed to determine the true risk based on today's available formulations. Providers should prescribe COC medications with an understanding of each patient's unique history and other independent risk factors such as gene mutations, family history, age, and obesity.

It is also important to discuss the reduced overall risk of endometrial and ovarian cancer (Collaborative Group on Hormonal Factors in Breast Cancer, 1996; Frangos et al., 2008; George et al., 2008; Haider and Shaw, 2004). The follow-up on the Nurse's Health Study mentioned earlier also reported a decrease in mortality rates from ovarian cancer in patients who used COC formulations ($p = .002$; Charlton et al., 2014). A 2008 meta-analysis of 45 different studies reported a significant correlation between duration of COC use and reduction in risk of ovarian cancer ($p < .0001$; Collaborative Group on Epidemiological Studies of Ovarian Cancer, 2008). The risk of endometrial cancer is also reduced, theoretically due to the suppression of endometrial growth through contraceptive cycle control. A 1999 Swedish case-control study noted that COC use decreased the risk of endometrial cancer by 30% and that this reduction was noticeable after 3 or more years of use (Weiderpass et al., 1999).

Other common risks and side effects

Other important questions include the risk of weight gain, common side effects, rare side effects, and use of OCPs with antibiotic medications. In 30% of patients, 1 kg to 2 kg of weight gain occur mostly due to fluid retention. Other common side effects include unscheduled bleeding, nausea, and breast tenderness. These symptoms except for unscheduled bleeding are lessened with decreased estrogen doses. Less common side effects include decreased libido, melasma, and mood changes (Junkins-Hopkins, 2010).

It is important to discuss the interactions of antibiotic medications with OCPs especially in women who utilize OCPs as their primary means of birth control. Since many antibiotic medications are inducers of 3A4, practitioners are concerned that OCP efficacy can be reduced with concurrent antibiotic medication use. However, according to the 2006 ACOG Practice Bulletin, pharmacokinetic evidence of reduced steroid levels with antibiotic medication use only exists for rifampin. Studies have failed to demonstrate similar findings for doxycycline, ampicillin, metronidazole, tetracycline, or quinolones (Kaunitz, 2006).

Table 1

COC formulations, efficacy and safety reported in current literature

	Duration of Study	Dosage Studied	Type of Study	Efficacy Results	Safety Results
<i>EE and DRSP (Yasmin)</i>					
Efficacy and safety of 3 mg DRSP/20 mcg EE oral contraceptive administered in 24/4 regimen in the treatment of acne vulgaris: A randomized, double-blind, placebo-controlled trial (Koltun et al., 2008).	Six 28-day cycle treatments (approximately 6 months)	3 mg DRSP/20 µg EE	Randomized double-blind placebo controlled trial (sponsored study)	COC group had 4.31 odds of clear/almost clear skin as assessed by investigators after six 28-day cycles compared with placebo ($p = .001$)	COC group experienced three most common AEs: metrorrhagia, headache, and nausea at a higher rate compared with placebo. COC group experienced one serious AE: depression (not drug-related according to authors)
Treatment of moderate acne vulgaris using a COC formulation that contain EE 20 µg plus DRSP 3mg administered in a 24/4 regimen: A pooled analysis (Koltun et al., 2011).	Six 28-day cycle treatments (approximately 6 months)	3 mg DRSP/20 µg EE	Pooled analysis of two large randomized placebo-controlled clinical trials (sponsored study)	Total, inflammatory, and non-inflammatory lesion counts were more greatly reduced for COC users vs. placebo by cycle 3 and at end point ($p < .0001$). COC group had approximately three times odds of clear/almost clear skin by endpoint compared with placebo by investigator assessment.	N/A
A single-center, randomized double-blind, parallel-group study to examine the safety and efficacy of 3 mg DRSP/0.02 mg EE compared with placebo in the treatment of moderate truncal acne vulgaris (Palli et al., 2013).	Six 28-day cycle treatments (approximately 6 months)	3 mg DRSP/20 µg EE	Randomized double-blind parallel-group study	COC group experienced significantly greater reductions in noninflammatory and total acne count by week 24 compared with placebo ($p = .02$).	No severe AEs were reported in the study.
<i>EE and DSG (e.g., Desogen, Novial, Oilezz, Mircette)</i>					
Effect of a DSG-containing oral contraceptive on the skin (Katz et al., 2000).	Six 28-day cycle treatments (approximately 6 months)	50/100/150 µg DSG and 35/30/30 µg EE given in a 7/7/7-day regimen	Double-blind placebo controlled pilot study	COC group had significant reduction in sebum production on cheeks compared with placebo. No differences seen in acne lesion count between groups. Both patient and physician assessment of skin condition (VAS) significantly better in COC group.	N/A
Effects of biphasic oral contraceptives containing DSG (Oilezz) on cycle control facial acne and seborrhea in healthy Thai women (Wonglikhitpanya and Taneepanichskul, 2006).	6 months	N/A	Prospective, open, non-comparative, single center study	Patients experienced significant improvements in facial seborrhea. A total of 80% of the COC group had complete clearance of acne.	No serious AEs reported
The effect of a phasic oral contraceptive containing DSG on seborrhea and acne (Kränzlin and Nap, 2006).	Four 28-day cycles (16 weeks)	50/100/150 µg DSG and 35/30/30 µg EE given in a 7/7/7-day regimen	Non-randomized group-comparative trial (sponsored study)	COC users experienced statistically significant reduction in sebum production compared to controls. No difference in acne reduction. Both investigators and patients reported better skin condition in COC group (VAS).	Most common AE in COC group was headache and 26.1% of users experienced irregular bleeding during the first cycle.
<i>EE and LNG (e.g., Lybrel, Alesse, Tri-levlen)</i>					
A randomized, controlled trial of a low-dose contraceptive containing 20 microg of EE and 100 microg of levonorgestrel for acne treatment (Thiboutot et al., 2001).	Six 28-day cycles (approximately 6 months)	20 µg of EE and 100 µg of LNG	Multicenter, randomized, double-blind, placebo-controlled clinical trial (Investigator-initiated)	By cycle 6, inflammatory, noninflammatory, and total lesion counts were significantly reduced in COC group compared with placebo ($p < .05$). Physician and patient assessments were also significantly better in COC group ($p = .016$, and $p < .05$).	Menorrhagia, metrorrhagia, menstrual disorder, and emotional lability was significantly higher in the COC group. One serious AE occurred in the COC group: depression (and hospitalization).
Efficacy of a low-dose oral contraceptive containing 20 microg of EE and 100 microg of LNG for the treatment of moderate acne: A randomized, placebo-controlled trial (Leyden et al., 2002).	Six 28-day cycles (approximately 6 months)	20 µg of EE and 100 µg of LNG	Randomized, double-blind, placebo-controlled clinical trial	Total and inflammatory acne lesion count ($p < .05$) clinician and patient assessments ($p < .05$), and biochemical androgenicity markers were improved in COC group compared with placebo.	N/A

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Table 1 (continued)

	Duration of Study	Dosage Studied	Type of Study	Efficacy Results	Safety Results
<i>EE and CMA (e.g., Belara)</i> Efficacy of an oral contraceptive containing EE 0.03 mg and CMA 2 mg (Belara) in moderate acne resolution: A randomized, double-blind, placebo-controlled Phase III trial (Plewig et al., 2009).	Six 28-day cycles (approximately 6 months)	EE 0.03 mg and CMA 2 mg	Randomized, double-blind, placebo-controlled Phase III trial (sponsored study)	Both papulopustular and comedonal acne was reduced in a significantly greater percentage of COC users compared with placebo ($p < .05$). Patient self-assessments were also superior in the COC group compared with placebo.	Headache, nausea, intermenstrual bleeding, breast pain, and fluor vaginalis were the most common AEs at a higher incidence in the COC group. Two severe AEs (ovarian cyst (possibly related) and influenza (not related)) were reported in the COC group.
Effects of an oral contraceptive that contains CMA and EE on acne-prone skin of women of different age groups: An open-label, single-center, phase IV study (Kerscher et al., 2008).	Six 28-day cycles (approximately 6 months)	CMA 2 mg and EE 0.03 mg	Open-label, prospective, single-center, phase IV study (sponsored study)	Statistically significant improvements in seborrhea and pore size in COC group compared with placebo after six cycles of treatment.	N/A
<i>EE and NGM (e.g., Ortho Tri-Cyclen, Vivelle)</i> Clinical evidence of the endocrinological influence of a triphasic oral contraceptive containing NGM and EE in women with acne vulgaris. A pilot study (Sator et al., 2003).	28-day cycles for 6 months	NGM (0.18 mg days 1–7; 0.216 mg days 8–14; 0.25 mg days 15–21) and EE (35 µg days 1–21)	Prospective single group (investigator-initiated)	At endpoint of 6 months, sex hormone profile improved, nine out of ten patients who completed study reported improvement, acne counts were reduced, and skin surface lipids were reduced.	Two patients withdrew: One patient reported headaches and intracyclic bleeding, one patient reported exhaustion. Two subjects who completed study experienced headaches and weight gain.

CMA, chlormadinone acetate; COC, combined oral contraceptive; DRSP, drospirenone; DSG, desogestrel; EE, ethinylestradiol; N/A, not applicable; LNG, levonorgestrel; NGM, norgestimate; VAS, visual analogue scale.

Contraindications of combined oral contraceptive formulations

Important contraindications to consider prior to the initiation of COC therapy include cardiovascular risk factors, severe hypertension, history of stroke, VTE or myocardial infarction, smoking combined with age >35 years, history of migraine with focal aura, history of migraine combined with age >35 years, current or past history of breast cancer or endometrial cancer, cholestatic jaundice of pregnancy (or jaundice with previous OCP use), diabetes with complications, hepatic neoplasias, abnormal liver function, hypersensitivity to OCPs, pregnancy, and major surgery with prolonged immobilization (Bonnema et al., 2010; Frangos et al., 2008).

Spirolactone

Spirolactone is an aldosterone antagonist that is often used as a diuretic and provides mortality benefit for patients with severe congestive heart failure. However, in higher doses, this agent also exhibits anti-androgen effects through inhibition of the cytochrome p450 system, inhibition of 5 alpha-reductase activity, and increase of hepatic synthesis of sex hormone-binding globulin (Armanini et al., 2016). Although not an FDA-approved medication for the treatment of acne, clinicians have often used this agent when there is inadequate acne control in patients who are already treated with a COC, have a contraindication to COC formulations, have coexisting hypertension, or their economic barriers prevent the purchase of other acne-controlling medications. The usual dosing of this medication is 50 to 200 mg/day. Contraindications to the use of spiro lactone include renal insufficiency, hyperkalemia, pregnancy, or unevaluated abnormal uterine bleeding (Zaenglein et al., 2016).

There have been no randomized prospective placebo controlled trials on the efficacy of spiro lactone in the treatment of adult-onset acne vulgaris. However, a few observational and retrospective analyses have been conducted in the last decade. These studies demonstrate excellent rates of efficacy for oral spiro lactone to treat female adult patients with acne. The treatment doses ranged from 100 to 200 mg/day. Sato et al. (2006) conducted a study in which 139 Japanese patients were treated with a 20-week tapered regimen of oral spiro lactone. A total of 64 female patients completed the study and there was a 100% response rate with approximately 50% of patients who had an excellent response. A total of 23 male patients were also initially included in the study but treatment was stopped after several men developed gynecomastia (Sato et al., 2006).

Yemisci et al. (2005) performed a similar study and demonstrated an 85% response rate with significant improvements in acne for responders. In another study on the effects of treatment with topical spiro lactone, 78 patients were enrolled in a randomized, double-blind, placebo controlled trial. The effects of 5% topical spiro lactone on acne were mixed with a significant decrease in total acne lesion count but no difference in acne severity index between the two groups (Afzali et al., 2012). In conclusion, on the basis of initial studies, oral spiro lactone demonstrates adequate levels of efficacy especially for patients with recalcitrant and/or severe forms of acne and those who have failed with COC therapy.

Spirolactone has also been studied in combination with other acne therapies including topical retinoids and COC formulations that contain drospirenone (Krunic et al., 2008; Lessner et al., 2014). Both studies demonstrated that combination treatment with these agents is both efficacious and well-tolerated. Although spiro lactone has been considered generally safe, there are certain common side effects including menstrual irregularities, breast tenderness, fatigue, and

Table 2
Head-to-head comparison studies of COC formulations in acne treatment

	Duration of Study	Type of Study	Dosages Studied	Results
<i>DSG and EE vs. LNG and EE</i>				
DSG + EE vs. LNG + EE. Which one has better effect on acne, hirsutism, and weight change (Sanam and Ziba, 2011B58).	1 year	Randomized clinical trial	30 µg EE, 0.15 mg progesterin (either DSG or LNG)	Both acne and hirsutism were more significantly improved in the DSG/EE group vs. the LNG/EE group ($p = .000$). Weight gain was significantly greater in the LNG/EE group ($p = .000$).
A randomized controlled trial of second-versus third-generation oral contraceptives in the treatment of acne vulgaris (Rosen et al., 2003).	9 months	Randomized control trial	30 µg EE, 0.15 mg progesterin (either DSG or LNG)	Mean acne lesion count was significantly reduced in both groups ($p < .02$). There was no statistically significant difference in acne lesion count reduction between the two groups (58.5% DSG vs. 52.8% LNG); limited power (5%).
Cycle control, quality of life and acne with two low-dose oral contraceptives containing 20 microg EE (Winkler et al., 2004).		Group-comparative, randomized, multicenter trial (sponsored study)	20 µg EE/0.15 mg DSG vs. 20 µg EE/0.10 mg LNG	The DSG/EE group had fewer acne lesions compared to the LNG/EE group at the endpoint of six cycles of treatment ($p < .05$).
<i>DSG/EE v.s CPA/EE</i>				
Comparison of the effect on acne with a combiphase DSG-containing oral contraceptive and a preparation containing CPA (Vartiainen et al., 2001).	Six 28-day cycles (approximately 6 months)	Open, randomized, group-comparative, multicenter study	First 7 days: 5 µg DSG/40 µg EE; After 15 days: 125 µg DSG/30 µg EE vs. 2 mg CPA/35 µg EE (for entire cycle)	Patients in both groups experienced statistically significant decreases in all acne lesion counts after cycle 3 and at the end of the 6-month study ($p \leq .003$). There were no significant differences in acne reduction between the groups.
<i>DSG/EE vs. NGM/EE</i>				
A comparison of multiphasic oral contraceptives containing NGM or DSG in acne treatment: A randomized trial (Jaisamrarn et al., 2014).	6 months	Investigator-blinded, randomized, parallel group trial, multicenter (investigator-initiated)	EE/DSG: days 1-7: 0.04 mg EE/0.025 mg DSG; days 8-22: 0.03 mg EE/0.125 mg DSG EE/NGM: days 1-7: 0.035 EE/0.18 NGM mg, days 8-14: 0.035 EE/0.215 NGM mg, days 15-21: 0.035 EE/0.25 NGM mg.	At the end of 6 months, no statistically significant differences were seen in acne lesion count reduction between the two groups. Percentage decreases in acne lesion count: EE/NGM: 74.4% vs. EE/DSG: 65.1%, $p = .070$
<i>CMA/EE vs. LNG/EE</i>				
Acne resolution rates: Results of a single-blind, randomized, controlled, parallel phase III trial with EE/CMA (Belara) and EE/LNG (Microgynon; Worret et al., 2001)	Twelve 28-day cycles (approximately 1 year)	Single-blind, randomized, controlled, parallel phase III trial (sponsored study)	0.03 mg EE/2 mg CMA vs. 0.03 mg EE/0.15 mg LNG	A greater percentage of CMA patients demonstrated at least a 50% reduction in papules and pustules by the 12 th treatment cycle (59.4% vs. 45.9% $p = .02$)
<i>CPA/EE vs. DRSP/EE</i>				
The effect of 2 combined oral contraceptives containing either DRSP or CPA on acne and seborrhea (van Vloten et al., 2002).	Nine 28-day cycles (approximately 9 months)	Multicenter, double-blind, randomized study	30 µg EE/3 mg DRSP vs. 35 µg EE/2 mg CPA	No significant differences in efficacy between CPA and DRSP formulations with both treatments achieving comparable lesion count reductions after nine cycles of treatment.
<i>CPA/EE vs. dienogest/EE</i>				
Efficacy of a combined oral contraceptive containing 0.030 mg EE/2 mg dienogest for the treatment of papulopustular acne in comparison with placebo and 0.035 mg ethinylestradiol/2 mg cyproterone acetate (Palombo-Kinne et al., 2009).	Six 28-day cycles (approximately 6 months)	Multinational, multicenter, three-arm, double-blind and randomized trial (investigator-initiated)	0.035 mg EE/2 mg CPA vs. 0.030 mg EE/2 mg DNG	EE/DNG was shown to be superior to placebo and non-inferior to EE/CPA in reducing acne lesion count ($p < .05$)
<i>CMA/EE vs. DRSP/EE</i>				
Effects of two estroprogestins containing EE 30 microg and DRSP 3 mg and EE 30 microg and CMA 2 mg on skin and hormonal hyperandrogenic manifestations (Lello et al., 2008).	6 months	Randomized clinical trial (investigator-initiated)	30 µg EE/3mg DRSP vs. 30 µg EE/2 mg CMA	Both groups demonstrated significant acne reduction from baseline ($p < .01$) by the end of study. The EE/DRSP response was better (faster and more prominent) at 3 months compared with the EE/CMA group ($p < .05$). The reduction in acne at 6 months was the same for both groups.

CMA, chlormadinone acetate; COC, combined oral contraceptive; CPA, cyproterone acetate; DRSP, drospirone; DSG, desogestrel; EE, ethinylestradiol; LNG, levonorgestrel; NGM, norgestimate.

headache (Shaw and White, 2002). Hyperkalemia and the necessity of potassium level monitoring has been a subject of controversy in previous years.

However, in 2015, Plovanič et al. published a landmark paper with the results of a retrospective analysis of hyperkalemia rates in women who were administered spironolactone from 2000 to 2014.

The researchers concluded that routine potassium monitoring in healthy women who take this medication is unnecessary. Healthy women were defined as women ages 18 to 45 years who were diagnosed with acne, with the exclusion of women with heart failure, on medication that affects the renin-angiotensin-aldosterone pathway, or who were diagnosed with renal disease (Plovovich et al., 2015). However, physicians should screen patients for bizarre diets that are high in potassium-containing substances such as coconut water prior to the initiation of spironolactone therapy.

Other safety considerations have included the effect of spironolactone on the body's thrombotic state. Unlike COC formulations, spironolactone seems to improve the thrombotic profile because aldosterone is known to be prothrombotic. Two individual case studies report the successful use of spironolactone-based treatment for Budd-Chiari syndrome in one patient with protein C deficiency and portal vein thrombosis in another patient with hepatitis B-related chronic liver disease (Hiroe et al., 2008; Kumar et al., 2011; Struthers and MacDonald, 2004).

At very high doses, spironolactone has also been associated with benign tumor formation in studies on animals. In a study on rats that were administered spironolactone at doses of 50, 150, and 500 mg/kg/day, increases in benign adenomas of the thyroid and testes were reported after 18 months. Similar doses in another study of rates led to the formation of hepatocellular adenomas in the subjects after 24 months, which caused the FDA to issue a black box warning (FDA, Aldactone Black Box Warning, revised 2008). However, long-term safety data does not support tumorigenic potential in humans (Danielson et al., 1982; Friedman and Ury, 1980; Shaw and White, 2002).

Flutamide

Flutamide is a selective androgen receptor antagonist, which is a well-known hormone-based chemotherapeutic agent to treat patients with prostate cancer. This agent has been purported as a potential therapy for adult onset acne vulgaris due to its antiandrogenic properties. However, very few studies on the efficacy of flutamide in acne treatment have been published thus far. A 2002 study conducted by Carmina and Lobo demonstrated the equal and significant efficacy of flutamide and a COC formulation (EE + cyproterone acetate) in the reduction of acne Cook scores in 48 hyperandrogenic women (Carmina and Lobo, 2002). However, the study did not directly assess the effects of flutamide in nonhyperandrogenic women who make up a significant portion of patients with adult acne.

Paradisi et al. (2011) published a retrospective study on the effects of low dose flutamide in patients with acne who were over 15 years of age. More than 97% of patients reported satisfaction with the control of their acne on low-dose flutamide regimens over a 6-year period (Paradisi et al., 2011). However, flutamide has been used cautiously by clinicians because of potential hepatotoxic effects. In the previous study, 5% of patients experienced significant increases in transaminase levels. The androgen excess group of the American Society for Reproductive Medicine noted that flutamide had very limited value in the treatment of hyperandrogenism because of its hepatotoxic effects (Fausser et al., 2012).

Metformin

Interestingly, this well known drug that has been used to treat patients with diabetes for years, has recently gained attention as a potential treatment for hormonal acne in patients with polycystic ovarian syndrome (PCOS). Levels of facial sebum production are positively correlated with levels of the hormone insulin-like growth factor 1 (IGF-1), which is already known to be correlated with acne severity in women. IGF-1 is known to stimulate androgenic hormone

production, which may explain this phenomenon (Vora et al., 2008). This finding is independent of a diagnosis of PCOS and suggests that targeting hyperinsulinemia and IGF-1-mediated metabolic changes may be potentially beneficial to patients outside of the PCOS population. Metformin has been shown to improve acne in several studies in patients with PCOS and hyperinsulinemia. It is thought to act by increasing insulin sensitivity and thereby reducing levels of IGF-1 and its downstream effects (Bubna, 2016).

Conclusion

Hormone therapy is a safe and effective option for women who suffer from adult acne. Most COC formulations demonstrate a certain level of efficacy in the treatment of patients with acne. Large meta-analyses that compared the different COC formulations do not demonstrate significant differences in efficacy between the formulations.

Limitations of this review of current studies include difficulty to meaningfully compare the trials that are included because outcome measures varied across the studies. Lesion counts, sebum production, and investigator and patient-assessments were a few of the efficacy measures that were reported. Also, none of the trials that were reported were against active comparators. Most studies did not use follicle-stimulating and/or luteinizing hormone ratios or measurements of insulin resistance as exclusion criteria for screening.

The most common side effects that were reported throughout the literature with the use of COC formulations included headache, menstrual irregularities, nausea, and breast tenderness, which are all common side effects that are expected with the use of low-dose COC formulations. Despite the relative safety of COC formulations, discussions on risks and side effects with individual patients is necessary to provide the safest and most beneficial care. Independent cardiovascular risk factors such as smoking, hypertension, and diabetes should be addressed. When discussing clotting risk, the increased risk of thrombophilia should be conveyed but contextualized because pregnancy confers a significantly higher risk of clotting. Although the FDA has issued warning labels for increased clotting risk with drospirenone-containing OCPs, a recent large prospective trial has shown that there is no increased clotting risk compared with other OCP formulations (Dinger et al., 2016). It is important to know the general risks, side effects, and contraindications of COC formulations prior to prescribing them as an acne treatment.

It is also important to inform patients that COC therapy improves acne over time. Most studies showed some improvement at 3 months of treatment and the greatest levels of improvement at 6 months. Oral spironolactone is a highly effective and safe option to treat patients with acne and contrary to prior practice potassium monitoring is not required in patients without a history of prior renal disease. Spironolactone may provide additional benefit in the treatment of patients with acne when used together with OCP. It is also a lower cost option for patients who cannot afford expensive oral isotretinoin therapy. Overall, anti-androgen therapy represents a safe and effective option for the treatment of patients with adult acne vulgaris and therapy should be prescribed on the basis of patient preference, cost, and individual patient characteristics because differences in effectiveness do not drastically vary from one formulation to another.

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